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GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent  
(BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR,  
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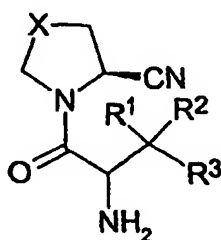
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*For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*

WO 03/002530 A3

(54) Title: PYRROLIDINES AS DIPEPTIDYL PEPTIDASE INHIBITORS



(I)

(57) Abstract: The present invention relates to novel compounds of formula (I), their use for inhibiting serine proteases, such as dipeptidyl peptidases, such as dipeptidyl peptidase IV (DPP-IV) and to methods for their production and their therapeutic utility.

## INTERNATIONAL SEARCH REPORT

International Application No  
PCT/US 02/20466

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7: C07D207/16 C07D277/06 A61K31/40 A61K31/426 A61P3/10

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, CHEM ABS Data

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	ASHWORTH D M ET AL: "4-Cyanothiazolidides as very potent, stable inhibitors of dipeptidyl peptidase IV" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, OXFORD, GB, vol. 6, no. 22, 19 November 1996 (1996-11-19), pages 2745-2748, XP004135888 ISSN: 0960-894X examples 3,6,7,9 examples 13-15; table II abstract  --- -/-	1,13,14, 16,20



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

## \* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

10 December 2002

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15. 01. 2003

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## INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 02/20466

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 95 15309 A (FERRING BV ;JENKINS PAUL D (GB); JONES D MICHAEL (GB); SZELKE MICH) 8 June 1995 (1995-06-08) cited in the application examples 19-23,27-29; table 2 tables 1-9 claims 2-5 ---	1,13,14, 16,20
P,X	WO 01 81304 A (EVANS DAVID MICHAEL ;PITT GARY ROBERT WILLIAM (GB); FERRING BV (NL) 1 November 2001 (2001-11-01) examples 20,21; table 1 examples 167,168; table 2 examples 263,264; table 3 examples 269,270; table 4 examples 335,336; table 5 examples 399,400; table 6 examples 1,2,4,7-9,12 tables 1-7 claims, 22-26 ---	1,16,20
P,X	WO 01 81337 A (EVANS DAVID MICHAEL ;PITT GARY ROBERT WILLIAM (GB); FERRING BV (NL) 1 November 2001 (2001-11-01) examples 1-3,6,10,11 example 16; table 1 example 38; table 2 tables 1,2 claims 9-15 ---	1,16,20
A	AUGUSTYNS K ET AL: "THE UNIQUE PROPERTIES OF DIPEPTIDYL-PEPTIDASE IV (DPP IV/CD26) AND THE THERAPEUTIC POTENTIAL OF DPP IV INHIBITORS" CURRENT MEDICINAL CHEMISTRY, BENTHAM SCIENCE PUBLISHERS BV, BE, vol. 6, no. 4, 1999, pages 311-327, XP000870290 ISSN: 0929-8673 abstract; examples 3-9 ---	1,16,20
E	EP 1 245 568 A (SERVIER LAB) 2 October 2002 (2002-10-02) examples 44,45,54,55,61,64,74,76 claims 12-14 ---	1,16,20
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	-/-	

## INTERNATIONAL SEARCH REPORT

International Application No

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## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>DATABASE CAPLUS 'Online!  CHEMICAL ABSTRACTS SERVICE, COLUMBUS,  OHIO, US;  KITASHIMA, HIROSHI ET AL: "Preparation of  N-(.alpha.-aminoacyl)-2-cyanopyrrolidine  derivatives as inhibitors of dipeptidyl  peptidase IV (DPP-IV) for drugs"  retrieved from STN  Database accession no. 137:232910  XP002224329  CAS RN: 459834-87-8; 459834-89-0;  459834-90-3; 459834-91-4; 459834-92-5;  459834-93-6; 459834-94-7; 459834-95-8;  459834-96-9; 459534-97-0; 459834-98-1;  459834-99-2; 459835-00-8; 459835-01-9;  459835-02-0; 459835-03-1; 459835-04-2;  459835-05-3; 459835-06-4; 459835-08-6;  459835-10-0  abstract</p>	1,16,20
E	<p>-&amp; JP 2002 265439 A (MITSUBISHI WELL  PHARMA K. K., JAPAN)  18 September 2002 (2002-09-18)  page 21 -page 23</p>	1,16,20
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X	<p>JIANG J D ET AL: "Inhibition of uman  immunodeficiency virus type 1 infection in  a T-cell line (CEM) by new  dipeptidyl-peptidase IV (CD26) inhibitors"  RESEARCH IN VIROLOGY, ELSEVIER, PARIS, FR,  vol. 4, no. 148, 1 July 1997 (1997-07-01),  pages 255-266, XP002074032  ISSN: 0923-2516  the whole document  figure 1</p>	1,16,20

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## INTERNATIONAL SEARCH REPORT

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## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>LI J ET AL: .  "AMINOACYLPYRROLIDINE-2-NITRILES: POTENT  AND STABLE INHIBITORS OF  DIPEPTIDYL-PEPTIDASE 4 (CD 26)"  ARCHIVES OF BIOCHEMISTRY AND BIOPHYSICS,  NEW YORK, US, US,  vol. 323, no. 1, October 1995 (1995-10),  pages 148-154, XP000965067  ISSN: 0003-9861  the whole document</p>	1,16,20
X	<p>LOREY S ET AL: "NEW FLUOROGENIC  DIPEPTIDYL PEPTIDASE IV/CD26 SUBSTRATES  AND INHIBITORS"  ADVANCES IN EXPERIMENTAL MEDICINE AND  BIOLOGY, SPRING ST., NY, US,  vol. 421, 1997, pages 157-160, XP001008342  ISSN: 0065-2598  table 2</p>	1,16,20
X	<p>EP 0 933 379 A (SHIONOGI &amp; CO)  4 August 1999 (1999-08-04)  page 54, line 24</p>	1
X	<p>WO 00 56297 A (BROQUA PIERRE ;FERRING BV  (NL)) 28 September 2000 (2000-09-28)  examples 1A,1B,  claim 1</p>	1,16,20
X	<p>STOECKEL-MASCHEK A ET AL: "POTENT  INHIBITORS OF DIPEPTIDYL PEPTIDASE IV AND  THEIR MECHANISMS OF INHIBITION"  ADVANCES IN EXPERIMENTAL MEDICINE AND  BIOLOGY, SPRING ST., NY, US,  vol. 477, 2000, pages 117-123, XP008000943  ISSN: 0065-2598  figure 3  tables 1,2</p>	1,16,20

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US 02/20466

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:  
  
Although claims 18-24 are directed to a diagnostic method practised on the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☒ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☒ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-4 (all partially); 5,6,11,  
12 (all completely); 13-33 (all partially)

Compounds according to formula (I) of claim 1 in which X represents -S(O)b- as well as their pharmaceutical use and compositions.

2. Claims: 1-4 (all partially); 7-10 (all completely); 13-33  
(all partially)

Compounds according to formula (I) of claim 1 in which X represents -CH<sub>2</sub>- as well as their pharmaceutical use and compositions.

## INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

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Information on patent family members

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